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# Asthma and Mode of Birth Delivery: A Study in 5-Year-Old Dutch Twins

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Several studies report caesarean section (CS) to be a risk factor for childhood asthma. We used data from a large cohort of 5-year-old twins to examine the relationship between mode of birth delivery and asthma. The extent to which an infant is exposed to maternal vaginal flora may protect against the risk of developing asthma. Therefore, we expect a lower rate of asthma in twins born by vaginal delivery (VD) than those born by CS, and a lower rate of asthma in first-born twins compared to second-born twins by VD. Information on mode of delivery was obtained at the time of birth in a survey completed by the mother shortly after delivery. Information on history of asthma diagnosis by a physician was obtained by parental report when the twins were 5 years old. Complete data were available for 6330 first-born and 5438 second-born twins from birth cohorts 1991–2000. Full term first-born twins born by CS had a significantly higher risk of asthma compared to those born by VD, odds ratio = 1.59 (95% CI = 1.23–2.06). No significant differences were observed between CS and VD first-born twins when gestational age was less than 37 weeks, and no significant differences were observed between CS and VD second-born twins at any gestational age. No differences in asthma prevalence were found between first- and second-born twins both born by VD. CS may increase the risk of asthma to full term infants, however, the underlying mechanism is unclear.

Several studies have examined the relation between caesarean section (CS) and asthma and associated allergic conditions. The results of these studies have been inconsistent. Some studies reported an increased risk of around 1.20 for asthma in children born after CS (Hakansson & Kallen, 2003; Kero et al., 2002; Laubereau et al., 2004; Salam et al., 2006), while others found no increased risk (Juhn et al., 2005; Maitra et al., 2004; McKeever et al., 2002; Werner et al., 2007; Xu et al., 2001). The largest effect was obtained by Xu et al. (2001), who reported an OR of 3.23.

In the present study we use twins as a unique population to examine the relationship between mode of birth delivery and risk of asthma. Using data from

twins may clarify the role of contact with maternal vaginal flora on asthma risk.

In our study we assume that first and second-born twins have a different degree of contact with maternal vaginal flora. This assumption is based on the results of a twin study on mother-to-infant transmission of the human immunodeficiency virus (HIV-1), where Goedert et al. (1991) found that first-born twins had a higher risk of infection than second-born twins after vaginal delivery (VD), but not after CS. They suggested that the first twin has greater exposure to secretions and blood compared to the second-born twin. Thus, if exposure to birth canal products plays an important role in triggering the initial bacterial colonization, and the subsequent development of the immune system, we expect to find a lower prevalence of asthma in VD first-born twins compared to VD second-born twins. Also, we expect that the prevalence of asthma will be higher in children born after CS compared to those born after VD, and that this difference will be greater in first-born than in second-born twins.

## Methods

### Participants and Measures

The data on birth delivery and asthma in twins come from a longitudinal study, which was designed to examine the genetic and environmental influences on the development of behavioral and emotional problems in twins from birth onwards. The twins' families are volunteer members of the Netherlands Twin Register (NTR), which is maintained by the Department of Biological Psychology at VU University in Amsterdam (Bartels et al., 2007; Boomsma et al., 2002, 2006). The NTR recruits families with twins a few months after birth. Around 40% of all multiple births in The Netherlands are registered by the NTR. For the present study, data included were obtained by surveys mailed to parents of twins at ages 1, 2, and 5 years.

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Shortly after registration of their newborn twins, mothers receive the first survey in which they are asked to report on mode of delivery, age at birth, gestational age, birthweight, birth order, sex of twins, and smoking behavior of both parents during pregnancy. On average, the mothers send this survey back within the first year after birth (mean age of twins = 8.4 months;  $SD = 13.85$ ). Information on birth delivery mode was available for twins born after 1990.

When the twins are 5 years old, the parents are asked to report (*yes/no*) whether a physician had diagnosed asthma (van Beijsterveldt & Boomsma, 2007b). From the same survey, information was obtained on current parental smoking, and the number of older siblings in the family. There were data for 9724 twin pairs with survey data at ages 1 and 5. Information on breastfeeding was obtained from survey data collected around the second birthday (Orlebeke et al., 1995).

We excluded data from twins who were born after vacuum/forceps delivery and twins born by VD in breech presentation (1772 first-born twins and 2685 second-born twins). Twins who were in breech presentation, but who were born by CS were included in the study. Twins with missing covariate information were excluded from the analyses. The final sample included 6330 first-born twins and 5438 second-born twins from birth cohorts 1991–2000.

#### Analyses

Comparisons of the characteristics between the CS and the VD group were performed separately for first- and second-born twins. Significance testing was done by chi-squared tests. Logistic regression was used to calculate the odds ratio (OR) and their 95% confidence intervals (95% CIs) for the association between mode of birth delivery and asthma. In a second step, all models were adjusted for the effects of maternal age at birth, smoking during pregnancy, current smoking, breastfeeding, sex, incubator time, and birthweight. In a second series of analyses, we compared the asthma prevalence between the first- and second-born twins. As there was a significant interaction between mode of delivery and gestational age for first-born twins ( $B = 0.273$ ,  $df = 1$ ,  $p = .038$ ), the results are given separately for twins with a gestational age of more than 36 weeks or less than 36 weeks. Significance testing was done by the McNemar chi-squared test to take into account the dependency within pairs.

#### Results

Table 1 shows the characteristics of mothers and twin offspring born after CS or VD. Twins born after CS had a shorter gestational age, older mothers, fewer older siblings, were less often been breast fed, stayed for a longer period in the incubator, and had a birthweight of 2000 gram or less more often than twins born by VD. Because these variables may act as possible confounders, they were included in the multivariate

**Table 1**

Child and Maternal Characteristics for Vaginal Deliveries (VD) and Caesarean Section (CS); Results ( $p$  values) of Chi-Squared Tests of the Comparisons of Child and Maternal Characteristics Between the VD and CS Groups

	VD %	CS %	$p$
Gestational age			
> = 37 weeks	62.0	58.6	
> 32 weeks and < 37 weeks	31.5	33.7	
< = 32 weeks	6.5	7.7	< .01
Maternal age			
< 30 years	38.4	36.1	
< = 30 and < 34 years	38.7	37.2	
> = 34 years	22.9	26.7	< .01
Smoking during pregnancy (mother)			
No	79.7	79.9	
Yes	20.3	20.1	.795
Current smoking parent			
No	60.6	60.9	
Yes	39.4	39.1	.762
Older siblings			
No	41.8	65.7	
Yes	58.2	34.3	< .01
Breastfeeding			
No	43.4	45.3	
1–6 weeks	25.3	27.8	
6 weeks–6 months	22.5	20.8	
> 6 months	8.7	6.1	< .01
Sex			
Boy	48.5	48.6	
Girl	51.5	51.4	.868
Incubator time			
No	60.6	44.8	
0.1–7 days	22.1	32.1	
8–14 days	8.3	9.4	
> 14 days	8.9	13.7	< .01
Birthweight			
> = 2000 gram	15.2	20.8	
< 2000 gram	84.8	79.2	< .01

models. The relationship between these confounders and asthma is described elsewhere in this issue (van Beijsterveldt & Boomsma, 2008).

In Table 2 the association between mode of birth delivery and asthma is given. For the pregnancies of 37 weeks or longer, first-born CS children had an increased risk for asthma in comparison to first-born VD children ( $OR = 1.46$ ,  $p < .01$ ). The effect remained significant after adjustment for confounding factors ( $OR = 1.59$ ,  $p < .01$ ). In contrast, for first-born twins of gestational age less than 37 weeks ( $OR = 0.96$ ,  $p = .754$ ), and for second-born twins of any gestational age, there was no difference in asthma prevalence between the CS and VD group.

We used McNemar chi-squared tests to test the prevalence differences between first- and second-born

**Table 2**

Relation Between Asthma and Mode of Birth Delivery for Term and Preterm Twins

	VD no asthma	%	Asthma	%	CS no asthma	%	Asthma	%	Odds ratio (95%CI)	Adjusted odds ratio (95%CI)
Gestational age $\geq 37$ weeks										
First-born										
Asthma at age 5	2419	92.5	195	7.5	1083	89.4	128	10.6	1.46 (1.16–1.85)	1.59 (1.23–2.06)
Second-born										
Asthma at age 5	1866	91.6	171	8.4	1182	91.9	104	9.1	0.96 (0.74–1.24)	0.91 (0.69–1.19)
Gestational age $\geq 37$ weeks and $> 32$ weeks										
First-born										
Asthma at age 5	1205	88.8	152	11.2	556	89.8	63	10.2	0.89 (0.66–1.23)	0.95 (0.68–1.31)
Second-born										
Asthma at age 5	896	89	111	11.0	619	89.8	70	10.2	0.91 (0.66–1.25)	0.92 (0.66–1.29)
Gestational age $\leq 32$ weeks										
First-born										
Asthma at age 5	254	83.8	49	16.2	125	84.5	23	15.5	0.95 (0.56–1.64)	0.88 (0.50–1.54)
Second-born										
Asthma at age 5	153	82.3	33	17.7	135	81.3	31	18.7	1.06 (0.62–1.83)	1.07 (0.61–1.90)

twins born (data not shown). No significant differences in asthma were found between the first- and second-born VD twins,  $\chi^2(1) = 0.350$ ;  $p = .554$ , but a significant difference was found between the first and second born twins both born after CS,  $\chi^2(1) = 5.786$ ;  $p = .016$ . Among twins born at term by CS, second-born twins had a lower prevalence of asthma compared to their first-born cotwins.

## Discussion

The main purpose of this study was to examine the association between mode of birth delivery and asthma in a large sample of young twin pairs. The data show that twins born by CS had a higher risk of developing asthma compared to twins born VD. However, this difference was only observed for first-born twins born at term. In addition, among twins born by CS at term, second-born twins had a lower risk of developing asthma in comparison to first-born twins. For twins delivered after VD, no difference in asthma prevalence between first- and second-born children was seen.

The increased risk of asthma for first-born twins born by CS is consistent with results of some non-twin studies that examined the risk of asthma and related conditions among children born by CS (Hakansson & Kallen, 2003; Kero et al., 2002; Salam et al., 2006). However, many methodological issues play a role in the interpretation of the results. Results may be biased by factors related to the sample, maternal and birth characteristics, and by the classification of the asthma and allergic conditions. For example, Juhn et al. (2005) performed a longitudinal study and compared the rate of asthma between children born by CS and VD during the first 7 years of life, and found that the relationship between mode of delivery and asthma varied over time. They observed an effect

of CS on asthma only during the first year of life. The inclusion of preterm infants may bias the association between mode of delivery and asthma because prematurity itself may be a risk factor for asthma. Debley et al. (2005) reported a significant association between CS and asthma hospitalization only in premature infants. Maternal asthma history could be another important confounder, as mothers with asthma more often require CS. Thus, the association between CS and asthma could be due to a genetic disposition for asthma.

In our study, CS births were associated with a smaller gestational age, older age of mother at birth, fewer older siblings, less breastfeeding, longer incubator time, and lower birthweight. Because these factors are associated with an increased risk for developing asthma, they are potential confounders for the association between CS and asthma. However, in the multivariate analyses that included these risk factors, we still observed a significant association between CS and asthma for first-born twins.

A limitation of this study is that we relied upon parent report of asthma and not on clinical assessment, which is less reliable. Also, we assessed asthma status at a relatively early age (5 years) when misclassification of asthma may be greater than it is in older children (Martinez et al., 1995). However, the advantage of the use of parental report is that asthma can be assessed in a large general population sample of twins.

In comparison with studies in singletons, the use of twin pairs provides additional opportunities for testing the association between mode of delivery and asthma. For example, we could examine the association between mode of delivery and asthma in both first- and second-born twins, which may clarify the role of vaginal contact in the association between CS and asthma. An important assumption that we have

made is that second-born twins have less exposure to maternal vaginal flora than first-born twins. For second-born twins with a gestational age of 37 weeks or more, the prevalence of asthma was slightly higher in the CS group (9.1%) than in the VD group (8.4%), but this difference was not significant. For first-born twins, the asthma prevalence in the CS group was also higher (10.6%) than in the VD group (7.5%) and in this group the difference was significant. In the VD group, the prevalence of asthma was lower in first-born than in second-born twins (7.5 vs. 8.4%), but this difference was not significant. Thus, the prevalence of asthma decreased with the extent of vaginal contact, but these prevalence differences were not significant. Therefore, it is uncertain whether the amount of contact with the maternal vaginal flora explains the association between CS and asthma.

The underlying mechanism for the association between asthma and CS is unclear. One of the explanations is the role of the intestinal flora in the development of the immune system (Björkstén et al., 1999; Kalliomaki et al., 2001). Björkstén et al. (1999) found that the composition of the intestinal microflora differed between allergic and nonallergic infants. In addition, there is evidence that the colonization of the intestinal flora is delayed in children born after CS compared to those born by vaginal delivery (VD) (Gronlund et al., 1999; Hallstrom et al., 2004; Ly et al., 2006). The differences in intestinal flora between CS and VD infants may be explained by differences in contact with the maternal vaginal flora during birth delivery (Ly et al., 2006).

Our results are compatible with this hypothesis, however there are complexities that require further exploration (for example, no difference in risk of asthma between first and second born twins both born by VD). Future research should assess microbacterial faeces in twins born after CS and VD.

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